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Association of Cardiac Troponin, CK-MB, and Postoperative Myocardial Ischemia With Long-Term Survival After Major Vascular Surgery

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OBJECTIVES The aim of this study was to determine the long-term prognosis with postoperative markers of myocardial ischemia and infarction.

BACKGROUND Cardiac troponins (cTn) are superior to creatine kinase-MB fraction (CK-MB) in detecting perioperative myocardial infarction (PMI). However, their threshold levels signifying PMI and their long-term prognostic value are not yet determined.

METHODS A cohort of 447 consecutive patients who underwent 501 major vascular procedures was prospectively studied. Perioperative continuous 12-lead electrocardiogram monitoring, cardiac troponin-I (cTn-I) and/or cardiac troponin-T (cTn-T), and CK-MB levels on the first three postoperative days, and long-term survival were determined. The association of different cutoff levels of CK-MB, troponin, and ischemia duration with long-term survival was investigated.

RESULTS Between 14 (2.9%) and 107 (23.9%) of the patients sustained PMI, depending on the biochemical criteria used. Elevated postoperative CK-MB, cTn, and prolonged (>30 min) ischemia, at all cutoff levels examined, predicted long-term mortality independent of the preoperative predictors: patient's age, type of vascular surgery, previous myocardial infarction, and renal failure (Cox multivariate analysis). Both CK-MB >10% and cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml independently predicted a 3.75-fold and 2.06-fold increase in long-term mortality ($p = 0.006$ and 0.012, respectively). Similarly, both CK-MB >5% and cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml independently predicted a 2.15-fold and 1.89-fold increase in mortality ($p = 0.018$ and 0.01, respectively). Patients with both these markers elevated had a 4.19-fold increase in mortality ($p < 0.001$).

CONCLUSIONS Postoperative CK-MB and troponin, even at low cutoff levels, are independent and complementary predictors of long-term mortality after major vascular surgery. (J Am Coll Cardiol 2003;42:1547–54) © 2003 by the American College of Cardiology Foundation

Postoperative myocardial infarction (MI) and major cardiac complications occur in more than 4% of the patients with either established diagnosis of coronary artery disease (CAD) or risk factors for CAD, who undergo major non-cardiac surgery (1,2). In the U.S., 1.5 to 2 million patients are at such risk for postoperative infarction each year (3). There is marked variability in the reported short-term mortality (<10% to 70%) (4–6), and there are very few data on the long-term prognosis after postoperative infarction (2,7,8). Unlike non-surgical MI, the clinical diagnosis of perioperative MI (PMI) is often difficult or even impossible, when based on the presence of two of the classical triad: cardiac symptoms, typical electrocardiographic (ECG) findings, and biochemical markers. The silent nature of perioperative infarction, the subtle and transient ST-depression ECG changes resulting in non–Q-wave infarction (4), and the claimed low specificity of creatine kinase-MB fraction (CK-MB) isoenzyme (9) all lead to inconsistencies in the diagnosis of PMI and to uncertainty as to the long-term significance of perioperative markers of MI.

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Cardiac troponins (cTn) are highly sensitive and specific biochemical markers for myocardial necrosis and predict increased risk of mortality and reinfarction in patients presenting with acute coronary syndrome (ACS) (10,11). In surgical patients too, cTn have been shown to identify postoperative MI better than CK-MB isoenzyme (4,9,12,13). However, in the absence of typical signs and symptoms of MI, the diagnosis of postoperative MI has to rely heavily on the rise and fall of biochemical markers, especially on cTn (14). It is yet unclear, however, whether postoperative infarction detected predominantly on the basis of these markers bears the same clinical and prognostic implications as non-surgical infarction and, therefore, requires similar surveillance and treatment. Moreover, whereas in non-surgical patients with unstable coronary syndromes even the smallest increase in cardiac troponin-I (cTn-I) or cardiac troponin-T (cTn-T) is associated with worse outcome (15), there is as of yet no consensus concerning the threshold levels of cTn signifying postoperative MI, leading researchers to use different concentrations for its diagnosis.

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CAD = coronary artery disease
CK-MB = creatine kinase-MB fraction
cTn = cardiac troponin
ECG = electrocardiogram/electrocardiograph/electrocardiographic
MI = myocardial infarction
PMI = perioperative myocardial infarction

The present study aims to determine whether elevated postoperative troponin levels have significant prognostic implications and to define the plasma concentrations of cTn-I and cTn-T and CK-MB that correlate with postoperative myocardial ischemia based on continuous 12-lead ECG monitoring and with long-term survival. This was prospectively examined in a large cohort of vascular surgery patients.

METHODS

After approval by the Institutional Review Board and informed consent, 447 consecutive patients who underwent 501 major vascular surgical procedures (231 carotid endarterectomies, 77 abdominal aortic operations, and 193 lower-extremity bypass procedures) at the Hadassah University Hospital from July 1997 to June 2001 were studied. The 49 patients who had more than one operation were included only once in the study. Those with no perioperative cardiac event or increase in cardiac markers were included on their first operation. If, however, one of the operations was complicated by a cardiac event or an increase in a cardiac marker, only that operation was included. None of the patients had unstable coronary syndrome in the three months preceding surgery. All preoperative chronic cardiovascular medications, including β-blockers and aspirin, were continued until the day of surgery and resumed as soon as possible postoperatively. After completion of surgery, patients were maintained in the recovery room or intensive care unit until at least the morning after surgery and were monitored with continuous intra-arterial blood pressure. The preoperative clinical findings and the perioperative cardiac complications were recorded prospectively.

Continuous 12-lead ECG recording. Continuous 12-lead ECG recording has been described previously (4). In brief, before induction of anesthesia, patients were connected to a continuous 12-lead ECG monitor (Solar 7000, Marquette Electronics, Milwaukee, Wisconsin), wired to a Cardiac Review Station (ST-Guard, Marquette Electronics), which automatically stored all 12-lead ECG complexes every minute and measured the absolute and relative ST-segment deviation at 60 milliseconds after the J point in all leads compared with their preoperative baseline. Episodes of ST-segment deviation, defined as ST depression or elevation of $\geq$0.2 mV in one lead or $\geq$0.1 mV in two contiguous leads that lasted more than 10 min, were automatically detected and marked by the ST-Guard. ST deviations lasting <10 min were ignored. Monitoring was continued for at least 48 h and up to 72 h. All 12-lead ST-segment trends were reviewed and periods marked by the ST-Guard, as ST-segment deviations were inspected visually and ST deviations caused by artifacts or pure up-sloping ST-segment depression were not considered as ischemia. Each patient's longest and cumulative ischemia duration, as well as the number of ischemic events was recorded.

Biochemical markers of MI. The cTn-I and/or cTn-T levels and CK-MB were measured in all patients immediately after surgery and every morning in the first three postoperative days. If either one of these markers was elevated, its measurement was continued for the next days until its return to normal values. Until January 1999 only troponin-I was available in our institution. From January 1999, cTn-T served as the primary indicator for MI, whereas cTn-I was used mainly for confirmation in patients with impaired renal function exhibiting high levels of troponin-T. Troponin-I was measured using a Stratus II analyzer (Dade-Behring, Inc., Marburg, Germany) by mass immunoassay with two monoclonal specific antibodies. Troponin-T was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 system (Boehringer Ingelheim GmbH, Germany).

Biochemical cutoff levels. Three different cutoff levels of cTn were examined: 1) cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml. These were the receiver operator characteristic curve medical decision cutoffs for MI defined by the manufacturers of these assays. 2) cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml, which correspond to the lowest levels with <10% imprecision or coefficient of variation for these assays (16). 3) cTn-I >3.1 ng/ml and/or cTn-T >0.2 ng/ml, which, based on previous studies including ours (4,5,9,17), showed a better correlation with postoperative ischemia and infarction.

The CK was measured by a Vitros dry chemistry analyzer (Ortho Clinical Diagnostics, Johnson & Johnson) using dry slide technology. The upper limit of normal for CK total was 170 IU. The upper limit of normal for CK-MB/total CK in our laboratory was 10%; however, the cutoff level of 5% that is more often used for defining MI (18) was also investigated.

Clinical cardiac complications. Clinical MI was diagnosed by the treating physicians independent of this study, if cTn-I >1.5 ng/ml and/or cTn-T >0.1 were associated with at least one of the following: typical ischemic symptoms, ECG changes indicative of ischemia, or new pathologic Q-waves (12). Prolonged chest pain, signs and symptoms of congestive heart failure, and new persistent arrhythmia were considered attributable to PMI if they were temporally associated with elevated cardiac markers. Cardiac death was defined as death secondary to MI, arrhythmia, or congestive heart failure.

Long-term survival. Long-term survival was recorded from the hospital's information system, which is constantly

Table 1. Preoperative Demographic and Clinical Data

	All Patients (N = 447) No. (%)
Age, yrs, mean ± SD [range]	68 ± 10 [39–92]
Gender (male/female)	312/135 (69.8/30.2)
Surgery	
CEA	214 (47.9)
AAA	70 (15.7)
Infra-inguinal BP	163 (36.5)
Diabetes mellitus	109 (24.4)
Hypertension	283 (63.3)
Hyperlipidemia	141 (31.5)
Smoking history	240 (53.7)
History of IHD	182 (40.7)
History of MI	116 (26.0)
Angina pectoris	76 (17.0)
Congestive heart failure	36 (8.0)
Previous PTCA	75 (16.8)
Previous CABG	90 (20.1)
Kidney disease, creatinine ≥2 mg/dl	13 (2.9)

AAA = abdominal aortic aneurysm; BP = bypass procedure; CABG = coronary artery bypass graft; CEA = carotid endarterectomy; IHD = ischemic heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

updated by the Israeli Ministry of the Interior with all newly deceased individuals along with the date of their death.

Statistical analyses. Chi-square analyses were used to compare dichotomous variables between groups of patients. Kaplan-Meier log-rank test and univariate and multivariate Cox regression models were used to compare survival among groups and to define predictors of long-term survival. All potential preoperative predictors with $p < 0.1$ on univariate survival analysis were included in the Cox multivariate regression analysis, and a backward conditional selection method was used for variable selection by the model. A value of $p \leq 0.05$ was considered statistically significant. All the analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

The demographic and preoperative clinical data on the 447 patients are summarized in Table 1.

Myocardial ischemia. During 25,622 patient-hours of continuous 12-lead ECG monitoring (51.4 ± 15.7 h/patient), 66 patients had 104 ischemic episodes; all but one were denoted only by ST-segment depression alone. One patient had episodes of ST depression in the chest leads associated with ST elevation in the inferior leads. The duration of the longest ischemic episode in each patient was 16 ± 62 min (range, 11 to 625 min), and the cumulative ischemia duration of each patient was 23 ± 101 min (range, 11 to 1,150 min). The longest ischemic episode lasted over 30 min in 44 (9.8%) of the patients and over 60 min in 23 (5.1%) of the patients.

MI. Between 14 (2.9%) and 107 (23.9%) of the patients sustained postoperative MI, depending on the biochemical criteria used (Table 2). Only 17.7% to 61.9% of them had signs or symptoms attributable to infarction. None of the patients had new Q-waves.

Each of the biochemical criteria for MI was associated with prolonged postoperative ischemia. The higher levels of troponin and CK-MB were associated with a higher incidence of prolonged postoperative ischemia (Table 2).

Sixteen (3.6%) patients were diagnosed by the treating physicians as having postoperative MI, based on the combination of elevated cTn with ECG findings and/or prolonged chest pain. Twelve (2.8%) of these patients had symptoms attributable to MI: five experienced chest pain, eight had congestive heart failure (one suffered from both). All 12 patients had both elevated cTn levels and prolonged (>60 min) postoperative ischemia. Two other patients died shortly after postoperative infarction (8 and 32 days postoperatively); none of them had typical symptoms of MI, and the diagnosis was made on the basis of the biochemical markers and the 12-lead ECG findings. Three additional patients died postoperatively from non-cardiac causes. All other patients left the hospital in stable condition.

Long-term survival. During the one- to five-year follow-up period (mean: 32.3 ± 13.8 months), 82 patients (18.3%) died. Table 3 summarizes the univariate and multivariate Cox survival analysis of the preoperative and postoperative predictors of survival. By multivariate Cox regression analysis, age, type of vascular surgery (lower-extremity bypass surgery), previous MI, and renal insufficiency were the only preoperative predictors of long-term survival.

All cutoff levels of CK-MB, cTn, and ischemia duration examined predicted long-term survival by univariate analysis (Figs. 1 to 3). Similarly, when the multivariate model included the preoperative predictors in addition to the

Table 2. Association of Longest Ischemia Duration With Biochemical Markers of MI

Myocardial Infarction Defined As	Total n (%)*	Ischemia >15 min n (%)†	Ischemia >30 min n (%)†	Ischemia >60 min n (%)†	Symptoms Attributable to MI‡
CK >170 IU and MB >5%	34 (6.7)	17 (50.0%)	14 (41.2)	12 (35.3)	7 (20.5)
CK >170 IU and MB >10%	14 (2.9)	8 (57.1)	7 (50.0)	7 (50.0)	5 (35.7)
cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml	107 (23.9)	34 (31.8)	29 (27.1)	21 (19.6)	19 (17.7)
cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml	41 (8.7)	38 (87.8)	24 (58.3)	19 (46.3)	18 (43.9)
cTn-I >3.1 ng/ml and/or cTn-T >0.2 ng/ml	21 (4.2)	19 (90.5)	17 (81.0)	17 (81.0)	13 (61.9)

*Percent of all 501 vascular operations. †All four biochemical criteria of infarction were significantly associated ($p < 0.001$) with both >30 min and >60 min ischemia duration using chi-square analysis. ‡Prolonged chest pain, congestive heart failure, or new onset arrhythmia.

CK = creatine kinase; cTn-I = cardiac troponin-I; cTn-T = cardiac troponin-T; IU = international units; MB = MB fraction; MI = myocardial infarction.

Table 3. Univariate and Multivariate Cox Regression Survival Analyses

		Univariate Analysis		Multivariate Analysis	
	Patients Who Died n (%)	Odds Ratio [95% CI]	p Value	Odds Ratio [95% CI]	p Value
Age		1.03 [1.01–1.05]	0.015	1.056 [1.01–1.09]	0.02
Gender (female)		0.66 [0.38–1.15]	0.14		
Type of surgery, compared with CEA	28 (13.3)				
Aorta	6 (8.6)	0.61 [0.29–1.49]	0.29	2.39 [0.93–6.13]	0.07
Lower-extremity bypass	47 (28.3)	2.32 [1.45–3.71]	< 0.001	2.52 [1.53–5.09]	0.008
Diabetes mellitus	33 (30.8)	1.74 [1.13–2.72]	0.017		
Hypertension	58 (20.3)	1.29 [0.78–2.15]	0.32		
Smoking history	34 (21.0)	0.94 [0.59–1.49]	0.83		
Hyperlipidemia	20 (14.1)	0.69 [0.19–4.90]	0.71		
Ischemic heart disease	38 (27.3)	2.34 [1.29–4.45]	0.004		
Previous myocardial infarction	32 (27.6)	1.80 [1.12–2.76]	0.008	1.88 [1.05–3.37]	0.034
Current angina pectoris	18 (27.7)	1.46 [0.86–2.49]	0.14		
Congestive heart failure	15 (41.7)	2.65 [1.50–4.65]	0.001		
Previous PTCA	15 (20.0)	1.05 [0.59–1.84]	0.86		
Previous CABG	21 (23.3)	1.23 [0.74–2.76]	0.43		
Kidney disease, creatinine ≥2 mg/dl	5 (38.5)	2.52 [1.02–6.23]	0.044	5.04 [1.89–13.43]	0.001
Perioperative infarction defined as					
CK >170 IU and MB > 5%	14 (41.2)	2.88 [1.62–5.11]	< 0.001	2.71 [1.48–4.98]*	0.001
CK >170 IU and MB > 10%	6 (42.8)	3.40 [1.48–7.81]	0.004	5.31 [2.21–12.78]*	< 0.001
cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml	37 (34.6)	2.30 [1.49–3.55]	< 0.001	2.15 [1.35–3.42]*	0.001
cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml	16 (39.0)	2.93 [1.75–4.89]	< 0.001	2.47 [1.44–4.23]*	0.001
cTn-I >3.1 ng/ml and/or cTn-T >0.2 ng/ml	11 (52.3)	3.41 [1.81–6.43]	< 0.001	2.93 [1.54–5.69]*	0.001
Longest ischemia duration (≥15 min)	66 (14.7)	2.15 [1.33–3.48]	0.002		
Longest ischemia duration (≥30 min)	18 (40.9)	3.05 [1.84–5.04]	< 0.001	2.59 [1.51–4.45]*	0.001
Longest ischemia duration (≥60 min)	13 (56.5)	4.35 [2.45–7.72]	< 0.001	3.75 [2.07–6.82]*	< 0.001

*Each one of the postoperative predictors was analyzed separately with the preoperative predictors in the multivariate analysis.
CABG = coronary artery bypass graft; CEA = carotid endarterectomy; CI = confidence interval; PTCA = percutaneous transluminal coronary angioplasty. Other abbreviations as in Table 2.

markers of infarction (each time a single marker was included in the model), the following markers independently predicted mortality, in the order of severity: 1) prolonged ischemia ≥60 min; 2) CK-MB >10%; 3) cTn-I >3.1 ng/ml and/or cTn-T >0.2 ng/ml; 4) CK-MB >5%; 5) prolonged ischemia ≥30 min; 6) cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml; and 7) cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml (Table 3).

When all postoperative markers of ischemia and infarction were included with the preoperative predictors in the multivariate analysis, only the following markers independently predicted mortality: 1) CK-MB >10%; 2) postoperative ischemia >60 min; and 3) cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml (odds ratio = 2.77, 2.20, and 1.64, p = 0.043, 0.033, and 0.054, respectively). If only the biochemical markers were included with the preoperative predictors in the multivariate analysis, both CK-MB >10% and cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml independently predicted mortality (odds ratio = 4.21 and 1.96, p = 0.002 and 0.005, respectively). If only the lowest cutoff levels of CK-MB and cTn were included, both CK-MB >5% and cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml independently predicted mortality (odds ratio = 2.14 and 1.89, p = 0.018 and 0.01, respectively). Finally, if the lowest cutoff levels of CK-MB and cTn were excluded from the multivariate analysis, both CK-MB >10% and cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml independently predicted mortality (odds ratio = 3.75 and 2.06, p = 0.006 and 0.012, respectively).

In additional analysis, patients who had both CK-MB >5% and cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml had a 4.19-fold increase in mortality (p = 0.001). Similarly, patients with both CK-MB >10% and cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml had a 4.04-fold increase in mortality (p = 0.007).

DISCUSSION

The main finding of the present study is that even minor elevations in cTn or CK-MB during the first three postoperative days predict increased risk of long-term mortality after major vascular surgery. Between 14 (2.9%) and 107 (23.9%) of the patients sustained postoperative MI or minor myocardial damage, depending on the cutoff levels of the biochemical marker. Higher levels of biochemical markers, corresponding to a larger volume of myocardial injury or infarction, predicted worse survival: CK-MB >10% and cTn-I >1.5 ng/ml and/or cTn-T >0.1 ng/ml predicted 3.75-fold and 2.06-fold increase in long-term mortality, independent of the preoperative predictors: patient's age, type of vascular surgery, previous MI, and renal failure; CK-MB >5% and cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml independently predicted a 2.15-fold and 1.89-fold increase in mortality. We have previously shown that

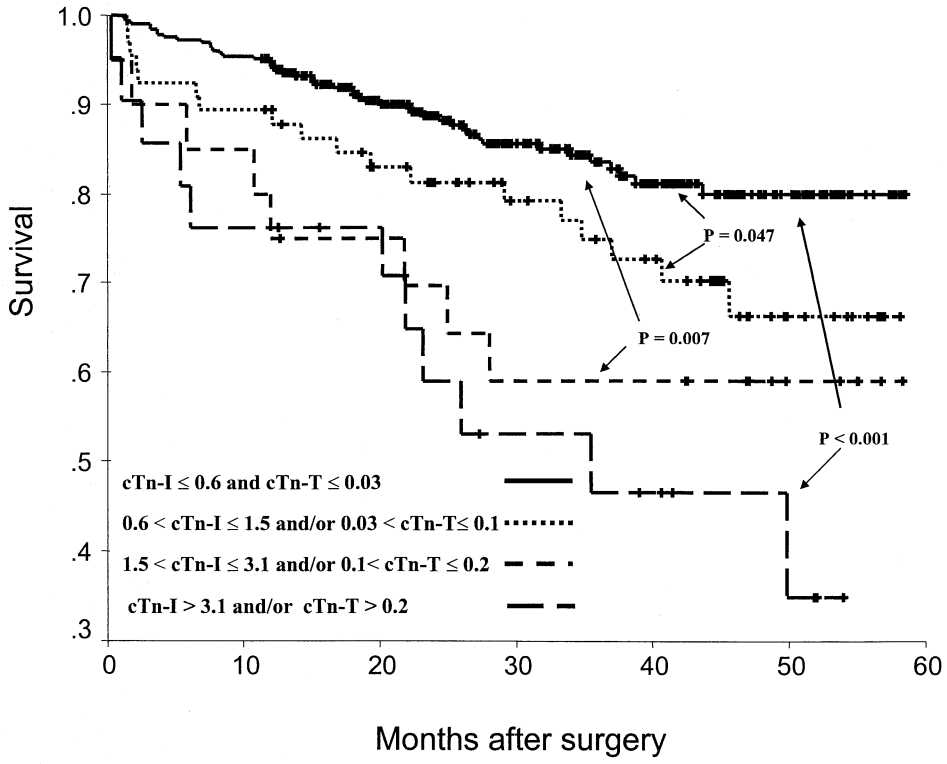

Figure 1. Kaplan-Meier survival curves of all patients divided according to their highest postoperative troponin level: Group I—cTn-I ≤ 0.6 ng/ml and cTn-T ≤ 0.03 ng/ml; Group II—0.6 ng/ml < cTn-I ≤ 1.5 ng/ml and/or 0.03 ng/ml < cTn-T ≤ 0.1 ng/ml; Group III—1.5 ng/ml < cTn-I ≤ 3.1 ng/ml and/or 0.1 ng/ml < cTn-T ≤ 0.2 ng/ml; Group IV—cTn-I > 3.1 ng/ml and/or cTn-T > 0.2 ng/ml; Groups II, III, and IV had worse long-term survival than Group I (p = 0.047, 0.007, and 0.001, respectively, by log-rank test). cTn = cardiac troponin.

prolonged, silent ST-depression-type postoperative ischemia leads to an elevation in troponin and to overt postoperative MI (4). In the present study too, prolonged postoperative ischemia and elevated troponin levels were strongly correlated (Table 2). Prolonged >30 min and >60 min postoperative ischemia was associated, respectively, with a 2.6-fold and 3.7-fold increase in adjusted long-term mortality (Table 3).

Two previous studies investigated the effect of postoperative cTn measurements on outcome after non-cardiac

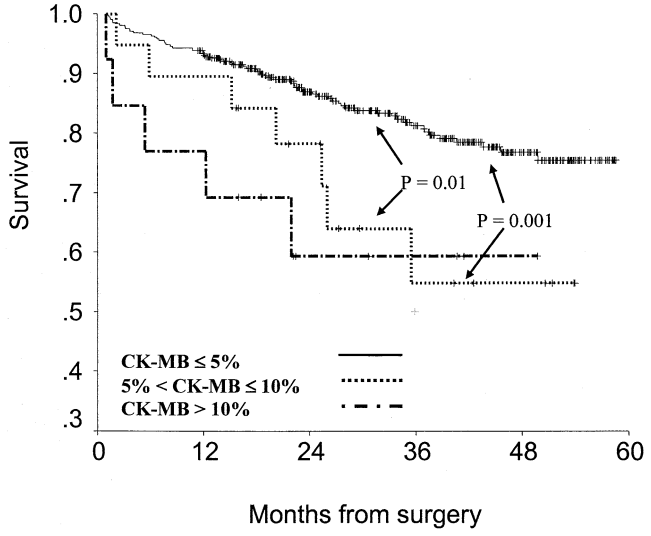

Figure 2. Kaplan-Meier survival curves of all patients divided according to their highest postoperative creatine kinase-MB fraction (CK-MB) level: Group I—CK-MB ≤5%; Group II—5% < CK-MB ≤10%; Group III—CK-MB >10%; Groups II and III had worse long-term survival than Group I (p = 0.01 and 0.001, respectively, by log-rank test).

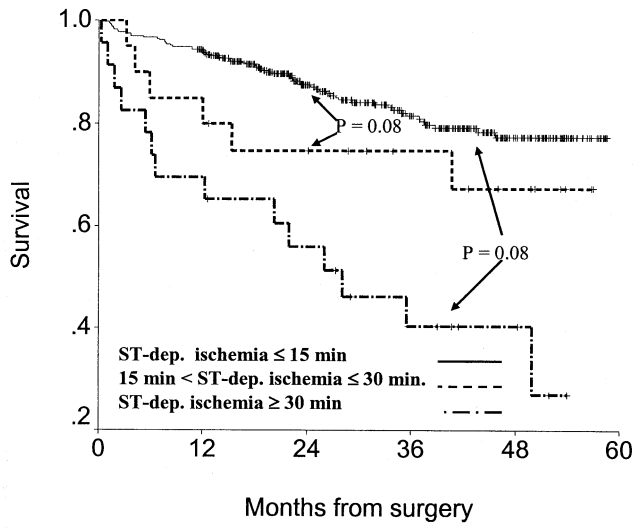

Figure 3. Kaplan-Meier survival curves of all patients divided according to their longest postoperative ischemia duration: Group I—ischemia duration <15 min; Group II—15 min < ischemia duration > 30 min; Group III—ischemia duration >30 min. Group III had worse long-term survival than Group I (p = 0.008, by log-rank test).

surgery, and both studies followed their patients for only six months after surgery. Lopez-Jimenez et al. (19) evaluated the prognostic significance of postoperative cTn-T on cardiac complications after non-cardiac surgery. In their study, troponin-T >0.1 ng/ml correlated with overall cardiac complications, which included cardiac death, nonfatal MI, or admission for unstable angina during the six months of follow-up. Abnormal CK-MB values were not associated with subsequent complications in that study. Recently, Kim et al. (20) showed that routine troponin-I measurement on the first three postoperative days predicted all-cause mortality in the first six months after vascular surgery. Yet, no comparison was made with the parallel measurements of CK-MB or ischemia duration. More importantly, 12 (67%) of the 18 patients who died during follow-up died within the first eight weeks after surgery, thus limiting the ability of that study to infer the effect of troponin on long-term survival. The present study corroborates and expands on those observations by its in-depth analysis of the biochemical markers as well as perioperative ischemia and by its longer duration of follow-up after surgery.

Troponin levels and MI. There is still an unresolved debate as to which cutoff levels of troponin should be used to define a clinically important MI. The conventional cutoff values, those obtained by titration of troponin to a population of patients with medical diagnosis of MI using receiver operator characteristic curve analyses, were troponin-I >1.5 and troponin-T >0.1 ng/ml for the assays used in our study. On the other hand, the American College of Cardiology/European Society of Cardiology task force stated in their consensus document for the redefinition of MI (14) that, because cTn are so specific to myocardial necrosis, even minor increases in troponin levels to greater than the 99th percentile of normal population, in the setting of documented myocardial ischemia, should be considered as MI. However, the level of precision of most troponin assays at this low range is still inadequate. Therefore, somewhat higher cutoff levels are suggested based on <10% imprecision or coefficient of variation. These levels of cTn-I >0.6 and cTn-T >0.03 ng/ml for our assays were used in the present study. Both the conventional cutoff levels, cTn-I >1.5 and/or cTn-T >0.1 ng/ml, by which 8.9% of the patients were identified as having postoperative MI, and the lower cutoff levels, cTn-I >0.6 and/or cTn-T >0.03 ng/ml, by which 23.9% of the patients had postoperative MI or minor myocardial damage, predicted long-term survival in accordance with recent findings in different kinds of patients with unstable coronary syndromes (21,22).

Troponin versus CK-MB. The CK-MB levels predicted long-term mortality independent of cTn. Fifteen (3.4%) patients had CK-MB >5% but troponin-I <0.6 ng/ml and troponin-T <0.03 ng/ml; 3 (20%) of these 15 patients died during follow-up. In comparison, 88 (19.6%) patients with elevated troponin (cTn-I >0.6 ng/ml and/or cTn-T >0.03 ng/ml) had normal postoperative CK-MB (<5%); 26 (29.5%) of them died during follow-up. Thus, troponin alone detected more patients with infarction and increased risk of mortality than CK-MB alone. It is important to note, however, that CK-MB >10% was associated with worse adjusted long-term survival than troponin-I >1.5 ng/ml and/or troponin-T >0.1 (odds ratio = 5.31 vs. 2.37, respectively), and similarly, CK-MB >5% predicted worse prognosis than the lower cutoff levels of troponin (Table 3). This observation may be explained by the higher sensitivity of troponin than CK-MB to even small MI or minimal necrosis, such that have less impact on prognosis than CK-MB. Whether CK-MB was more sensitive than troponin in detecting myocardial necrosis in a minority (3.4%) of the patients without increase in troponin, or reflected skeletal muscle injury due to more extensive surgery or lower-extremity ischemia and therefore worse survival (skeletal muscle may contain up to 10% CK-MB [23]), could not be determined by this study. However, patients with both elevated CK-MB and troponin had a 4.19-fold increase in mortality, whereas patients with only one of these markers had a 2.0- to 2.2-fold increase in mortality.

Clinically evident infarction. Only 25 (5.6%) of the patients satisfied the conventional clinical definition of MI according to the World Health Organization, i.e., the existence of at least two of the three criteria: prolonged chest pain, elevated CK-MB or cTn, and ischemic ECG changes (24). However, even in these patients the diagnosis of MI was not possible unless there was routine postoperative measurement of biochemical markers and continuous ECG monitoring, because only 16 (3.6%) of the patients had prolonged chest pain or congestive heart failure suspicious of overt MI. Our data corroborate those published by Kim et al. (20) wherein 12% of the patients had elevated troponin-I on routine postoperative surveillance, yet only 3% had clinical infarction according to the World Health Organization definition. Therefore, routine monitoring of cTn, CK-MB, and silent ischemia in the first postoperative days may provide important information on both the short-term and long-term risk of major vascular surgery patients.

The present study is also significant from the aspect of the pathophysiology of PMI. Recent studies have emphasized the prognostic importance of even minor elevations of cTn in patients with unstable coronary syndromes. Patients undergoing elective major vascular surgery constitute a different type of cardiac patients than those with unstable coronary syndromes. The former often have long-standing, yet stable CAD, and their postoperative cardiac events are typically caused by stress-induced, ST-depression-type ischemia leading to infarction (4). It has been long debated whether this type of silent postoperative ischemia and infarction is as prognostically meaningful as an ACS. In contrast to the older literature that cited 36% to 70% in-hospital mortality after PMI (25), current data show that early mortality after perioperative infarction is less than 10%, similar to that of non-ST-elevation-type infarction in non-surgical patients (4,19). This study further shows that

long-term survival after even minor perioperative infarction is significantly impaired, in line with what occurs after ACS in non-surgical patients.

Study limitations. Routine biochemical markers were measured only on the first three postoperative days. Therefore, MI evolving later than the third postoperative day may have been missed by our study protocol. However, previous studies have shown that the majority (>80%) of postoperative MI occur on the first two days after surgery (3,4,5,19). Therefore, although extending the biochemical marker measurements to the rest of the convalescence period could possibly identify more patients at increased risk for long-term mortality, it was not likely to affect the main findings of our study significantly.

We did not investigate the causes of the long-term deaths. Although the availability of such data could strengthen the study, numerous previous studies showed that the majority of deaths in vascular surgery patients are cardiac in nature and that close to half of the other non-cardiac causes of death are cardiovascular (26–29). Because not all our patients were prospectively followed for the entire follow-up period, we felt that retrospective collection of the causes of death might introduce significant inaccuracy to our data.

Although in the vast majority of postoperative patients the elevation of cardiac-specific markers is due to ischemic heart disease, there may be other clinical conditions such as pulmonary embolism, sepsis and renal failure, that may cause elevations of these markers and lead to an adverse prognosis.

Conclusions. Cardiac troponin, CK-MB, and prolonged postoperative ischemia predict long-term mortality after major vascular surgery. Troponin and CK-MB have an independent effect on long-term survival, and the combination of both is associated with even worse survival. Further studies are needed to test whether routine measurement of postoperative cardiac markers is cost-effective and whether more aggressive diagnostic and treatment strategies for patients with postoperative MI improve survival.

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